New claims 93-122 are added. Support for new claims 93-112 is found throughout the specification, particularly at: page 1, lines 33 through page 2, line 33; page 4, line 13 through page 5, line 18. Support for new claims 113-122 is found throughout the specification, particularly at: page 6, line 6 through page 9, line 11.

The first page of the specification has been amended to insert the proper priority claim.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

No new matter is added by any of the amendments. Accordingly, their entry by the Examiner is respectfully requested.

Priority

The Office Action has stated that Applicants have not complied with one or more condition for receiving benefit of an earlier filing date under 35 U.S.C. ' 120 because the first sentence of the specification does not contain a specific reference to the earlier applications. Applicants have amended the specification to use the phrase "claims the benefit of" in reference to provisional applications as requested by the Examiner. As such, Applicants respectfully request withdrawal of this objection.

Sequence Listing

Applicants acknowledge that the computer readable sequence listing has been entered without errors.

Rejection Under 35 U.S.C. §101

Claims 61-68 and 77-84 have been rejected under 35 U.S.C. §101 for the asserted reason that the claimed invention is not supported by either a specific and substantial utility or a well-established utility. The Office Action asserts that the claimed nucleic acids are not supported by a specific asserted utility because the disclosed uses of the nucleic acids as probes for isolation of full length cDNAs or genes, gene mapping, isolation of homologous sequences, detection of gene expression, molecular weight markers, chromosomal markers, and numerous other genetic engineering uses are not specific and are generally applicable to any nucleic acid. The Office

Action further claims that the subject nucleic acids are not supported by a substantial utility, stating:

> The research contemplated by applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a >real world= context or use. Similarly, the other listed and asserted utilities...are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Office Action, page 5.

In addition, the Office Action states that neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid such that another non-asserted utility would be well-established for the compounds. This rejection is traversed as applied and as it may apply to the presently pending claims.

The Office Action has noted that SEQ ID NOS: 730, 731, 919, 972, 973, 1128, 1254 and 1492 have a disclosed specific utility as a diagnostic since the specification establishes that they are differentially expressed in cancer cells. Applicants have attached a Declaration under 37 C.F.R. § 1.132 by Dr. Randazzo and Dr. Lamson, providing evidence or further evidence that SEQ ID NOS:730, 731, 972, 973, 1192, 1254 and 1492 represent genes that are differentially expressed in cancer cells (see Exhibit 1). Therefore, it follows that a polynucleotide having a sequence of SEQ ID NO:1192 also has a specific utility as a diagnostic.

In short -- and to summarize in a simplified manner-- the claimed polynucleotides represent genes differentially expressed in cancerous cells and/or represent genes expressed in a cancerous cell (*e.g.*, the polynucleotides were isolated from cDNA libraries of a cancerous cell line, see Example 1). Genes that are expressed in a cancerous cell have utility as, for example, encoding a therapeutic target. Genes that are differentially expressed between cancerous and normal cells have utility in, for example, diagnostics for detection of a cancerous cell.

In view of the specific utility of the sequences, Applicants respectfully request that the rejection of claims 61-68 and 77-84 under 35 U.S.C. § 101 be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 61-68 and 77-84 have also been rejected under 35 U.S.C. § 112, first paragraph, because one would not know how to use an invention that is not supported by either a specific

and substantial utility or a well-established utility. This rejection is traversed as applied and as it may apply to the presently pending claims.

As demonstrated above, each of the claimed polynucleotides correspond to a gene that is differentially expressed in cancer cells and have a specific utility as, for example, a diagnostic. One skilled in the art would know how to use the claimed differentially expressed sequences as diagnostics. As such, this rejection of claims 61-68 and 77-84 under 35 U.S.C. § 112, first paragraph, may be withdrawn.

Claims 20, 28, 36, 44, 52, 60, 68, 76, 84, and 92 have been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action asserts that the conditions for deposit of the claimed cells do not satisfy the requirements of 37 C.F.R. § 1.808 because a statement has not been made that restrictions on availability will be irrevocably removed upon granting of a patent.

Applicants have enclosed a Statement by Attorney for Applicant Regarding Permanence and Availability of Deposited Biological Materials with this response that confirms that the deposit requirements recited by the Examiner in the present Office Action have been met (see Exhibit 2). Accordingly, Applicants respectfully request that this rejections of claims 20, 28, 36, 44, 52, 60, 68, 76, 84, and 92 under 35 U.S.C. § 112, first paragraph, be withdrawn in view of the accompanying declaration.

Claims 13-92 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action asserts that the specification provides insufficient written description to support the genus of nucleic acid sequences encompassed by the claims, which include full length cDNA, sequences that hybridize to SEQ ID NOS:730, 731, 919, 972, 973, 1128, 1192, 1254, 1290 and 1492, sequences from other species, mutated sequences, allelic variants, and splice variants. The Office Action further claims that with the exception of the specific SEQ ID NOS, the skilled artisan cannot envision

the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. This rejection is traversed as applied and as it may apply to the presently pending claims.

The presently pending claims are directed to polynucleotides, cDNAs, recombinant host cells, vectors, polynucleotide sequences of inserts contained in ATCC deposited clones, polypeptides, and cDNAs produced by amplification using a fragment of a specific sequence. The polynucleotide sequences that are the basis for these claims were selected for their differential expression in cancerous cells relative to normal, non-cancerous cells. Applicants submit that one of ordinary skill in the art would recognize that they were in possession of the claimed subject matter at the time the invention was made.

The Office Action cites several cases in support of the assertion that the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides regardless of the complexity or simplicity of the method of isolation, and that an adequate written description requires the nucleic acid sequence itself. It is well established that the adequacy of a written description is judged as of the time of filing of an application.[1] Applicants note that the patents at issue in the cited cases were based on applications filed in the relative dark ages of biotechnology and that there have been many advances since that time.

For example, at issue in Amgen, Inc. v. Chugai Pharmaceutical Co., were U.S. Patent Nos. 4,703,008 and 4,677,195.[2] The 4,703,008 patent issued from an application filed on November 30, 1984; the 4,677,195 patent issued from an application filed on January 11, 1985. In another case cited by the Office Action, Fiers v. Revel, the disputed patent applications were filed in the late 1970's and early 1980's.[3] Furthermore, the disputed patent application in Fiddes v. Baird was filed in 1985 and the disputed patents were based on applications filed in 1985 and 1986. Finally, in University of California v. Eli Lilly and Co. the patents issued from applications filed in the late 1970's.[4] Clearly, the applications evaluated by the Court were filed many years ago.

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[1] Vas-Cath Inc. v. Mahurkar, 935 F. 2d 1555 (Fed. Cir. 1991).

[2] 927 F. 2d 1200, 1202 (Fed. Cir. 1991).

[3] 984 F. 2d 1164, 1167-1168 (Fed. Cir. 1993).

[4] 30 USPQ 2d 1481 (BPAI 1993); 119 F.3d 1559, 1562-63 (Fed. Cir. 1997), respectively

Recombinant techniques that are now routine were difficult to carry out at the time of filing of the above applications. For example, the Court in Amgen relies in part on the state of the art in holding that a method for isolating a specific gene did not satisfy the written description for obtaining that gene. The Court stated: "Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known. [that this] generalized approach would result in cloning the EPO gene."[5] However, it is now routine in the art to probe cDNA libraries with hybridization probes to isolate full-length cDNAs and, subsequently, the corresponding gene.

In addition, Applicants have provided two species for each claimed genus of nucleic acids: the specific SEQ ID NO and the ATCC-deposited clone containing that sequence. The courts have long recognized that every species in a genus need not be described in order that a genus meet the written description requirement.[6] All that is generally required is that Applicants disclose a representative number of species to justify claims to an entire genus.[7] Here, the two disclosed species for each genus are ample representation of the claimed genus to fulfill the written description requirement.

With respect to the scope of claims that can be allowed in view of the present state of the law, Applicants draw the Examiner's attention to U.S. Patent No. 5,861,248 ('248), which was filed on March 29, 1996 and issued on January 19, 1999 (copy enclosed). This patent discloses and broadly claims ESTs for genes that are differentially expressed in human prostate cancers as compared to normal prostate cells. The court decisions cited by the Office Action were all decided prior to the granting of the above patent. The claims of the '248 patent were granted by the Office in light of the same case law to which the present application is subject. Since the Office has held that the Applicants of the '248 patent had possession of their claimed invention, and the scope of the disclosure with respect to the sequence is similar to that provided by the

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[5] 927 F. 2d at 1207.

[6] See, e.g., Utter v. Haraga, 845 F. 2d 993, 998-99 (Fed. Cir. 1988) ("A specification may, within the meaning of § 112 P1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.")

[7] Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997) (stating that "A description of a genus of cDNAs may be achieved by means of the recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus...")

present application, then the Office should again recognize that Applicants of the present invention likewise had possession of their claimed invention at the time of filing and allow claims of similar scope, *i.e.*, allow claims that recite "comprising."

Requiring that Applicants use "consisting of" or "consisting essentially of" transitional language would unfairly limit the scope of Applicants claims. Under this language, a potential infringer could easily avoid infringement by slightly altering the patented gene sequence. Allowing such easy avoidance of infringement contravenes the public policy of the patent laws and the U.S. Constitution "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[8] By identifying and sequencing polynucleotides that are differentially expressed and disclosing two species of each claimed genus, Applicants are entitled to broader patent protection than such restrictive language would allow.

Finally, Applicants have added product-by-process claims to isolated cDNAs obtained by the process of amplification using a polynucleotide comprising at least a specified number of contiguous nucleotides of one of the disclosed SEQ ID NOS. Amplification of polynucleotides using methods such as PCR are well-known in the art and standard practice for the skilled artisan. In addition, methods of amplifying DNA are disclosed in the specification of the present application at, for example, page 6, line 6 through page 9, line 11. Furthermore, as disclosed in Example 10 of the Revised Interim Written Description Guidelines Training Materials, product-by-process claims have been found to be an acceptable way of claiming a broad genus when there is substantial variation within the genus.[9]

In sum, the state of the art has advanced to the point that Applicants= disclosure of two representative members of each claimed genus is sufficient for one of ordinary skill in the art to recognize that Applicants were in possession of the claimed invention at the time the application

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[8] U.S. Constitution, Article I, § 8, cl. 8

[9] These training materials were available via the USPTO website as of March 1, 2000; *See also* Amgen, 927 F.2d at 1206 (stating, "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it."); Fiers v. Revel, 984 F.2d at 1169.

was filed. As such, Applicants respectfully request that this rejection of claims 13-92 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 102(a)

Claims 77-79, 82, and 84 have been rejected under 35 U.S.C. §102(a) as being anticipated by GenBank Accession Number AA544005.

This rejection is obviated by the cancellation of claim 78 and the amendment to claims 77 and 79 to delete reference to 90% sequence identity and to specify that the claimed nucleic acid molecule comprises at least 35 contiguous nucleotides. The maximum number of contiguous nucleotides of GenBank Accession Number AA544005 that are identical to SEQ ID NO: 1290 is 32. Thus, the claimed sequences are not anticipated by GenBank Accession Number AA544005. As such, Applicants respectfully request that this rejection of claims 77-79, 82, and 84 under 35 U.S.C. §102(a) be withdrawn.

Sets of claims 13-15, 18, and 20: 21-23, 26, and 28; 29-31, 34, and 36; 37-39, 42, and 44; 45-47, 50, and 52; 53-55, 58, and 60; 61-63, 66, and 68; 69-71, 74, and 76; and 85-87, 90, and 92 have been rejected under 35 U.S.C. § 102(a) as being anticipated by GenBank Accession Numbers M15796, M88458, AA068559, AA131908, A050390, W89528, HSU58766, S82472, and H93085, respectively.

These rejections have been obviated by the cancellation of claims 14, 22, 30, 38, 46, 54, 62, 70, and 86 and the amendment to claims 13, 15, 21, 23, 29, 31, 37, 39, 45, 47, 53, 55, 61, 63, 69, 71, 85, and 87 to delete reference to 90% sequence identity and to specify that the claimed nucleic acid molecule comprises at least a specific number of contiguous nucleotides. The claim number, SEQ ID NO, GenBank Accession Number, specific number of contiguous nucleotides claimed, and the number of identical nucleotides of the corresponding GenBank Accession Number are summarized in the following table:

Claim Numbers	**SEQ ID NO**	**GenBank Accession Number**	**Claimed contiguous nucleotides: at least**	**GenBank contiguous nucleotides**
13, 15	730	M15796	150	120

Claim Numbers	SEQ ID NO	GenBank Accession Number	Claimed contiguous nucleotides: at least	GenBank contiguous nucleotides
21, 23	731	M88458	250	215
29, 31	919	AA068559	50	38
37, 39	972	AA131908	150	100
45, 47	973	A050390	35	24
53, 55	1128	W89528	100	53
61, 63	1192	HSU58766	100	85
69, 71	1254	S82472	150	108
85, 87	1492	H93085	100	76

As the above table shows, each set of claims specifies a longer set of contiguous nucleotides than are identical between each SEQ ID NO and the respective GenBank Accession Number. Thus, the claimed sequences are not anticipated by the above GenBank Accession Numbers. As such, Applicants respectfully request that this rejection of Sets of claims 13-15, 18, and 20; 21-23, 26, and 28; 29-31, 34, and 36; 37-39, 42, and 44; 45-47, 50, and 52; 53-55, 58, and 60; 61-63, 66, and 68; 69-71, 74, and 76; and 85-87, 90, and 92 under 35 U.S.C. ' 102(a) be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Sets of claims 16, 17, and 19; 24, 25, and 27; 32, 33, and 35; 40, 41, and 43; 48, 49, and 51; 56, 57, and 59; 64, 65, and 67; 72, 73, and 75; 80, 81, and 83; and 88, 89, and 91 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over GenBank Accession Numbers M15796, M88458, AA068559, AA131908, A050390, W89528, HSU58766, S82472, AA544005 and H93085, each in view of Yang et al. The Office Action asserts that it would have been obvious to a person skilled in the art at the time the invention was made to use the nucleic acid sequences of SEQ ID NOS:730, 731, 919, 972, 973, 1128, 1192, 1254, 1290 and 1492 as taught in GenBank Accession Numbers M15796, M88458, AA068559, AA131908, A050390, W89528,

HSU58766, S82472, AA544005 and H93085, respectively, in the yeast two-hybrid assay of Yang et al. and to isolate the encoded proteins of the SEQ ID NOS to test for binding to target proteins *in vitro* as taught by Yang et al. This rejection is traversed as applied and as it may apply to the presently pending claims.

The rejected claims are dependent on, or utilize, the polynucleotide of claims 13, 21, 29, 37, 45, 53, 61, 69, 77, and 85, respectively. As demonstrated above, these claims have been amended such that the claimed sequences are novel over the sequences of the corresponding GenBank Accession Numbers. Yang et al. describes a two-hybrid assay to detect protein-peptide interactions. The method of Yang et al. involves incorporating nucleotides into plasmids, generating libraries using *E. coli* cells, and expressing the encoded peptides. However, one of skill in the art could not have performed these steps with the claimed polynucleotides because the claimed polynucleotides were unknown before being described by Applicants in the present application.

Thus, sets of claims 16, 17, and 19; 24, 25, and 27; 32, 33, and 35; 40, 41, and 43; 48, 49, and 51; 56, 57, and 59; 64, 65, and 67; 72, 73, and 75; 80, 81, and 83; and 88, 89, and 91 are not obvious over the cited GenBank Accession Numbers in view of Yang et al. and this rejection under 35 U.S.C. § 103(a) may be withdrawn.

Conclusion

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

This response is being filed with a Petition for a Three Month Extension of Time, a Fee Transmittal sheet and authorization to charge Deposit Account No. 50-0815 for the requisite fees. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extension of time, or credit any overpayment to Deposit Account No. 50-0815, order number 23001487.

Respectfully submitted,

Date: May 31, 2001

By: _____
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Enclosures:

1) Statement by Attorney for Applicant Regarding Permanence and Availability of Deposited Biological Materials.
2) Declaration of Filippo M. Randazzo and George Lamson under 37 C.F.R. § 1.132.
3) U.S. Patent No. 5,861,248

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

13. (Amended) An isolated polynucleotide comprising at least [15] 150 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:730, a degenerate variant of SEQ ID NO:730, and a complement of SEQ ID NO:730.

15. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 150 contiguous nucleotides of the polynucleotide of claim 13.

21. (Amended) An isolated polynucleotide comprising at least [15] 250 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:731, a degenerate variant of SEQ ID NO:731, and a complement of SEQ ID NO:731.

23. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 250 contiguous nucleotides of the polynucleotide of claim 21.

29. (Amended) An isolated polynucleotide comprising at least [15] 50 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:919, a degenerate variant of SEQ ID NO:919, and a complement of SEQ ID NO:919.

31. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 50 contiguous nucleotides of the polynucleotide of claim 29.

37. (Amended) An isolated polynucleotide comprising at least [15] 150 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:972, a degenerate variant of SEQ ID NO:972, and a complement of SEQ ID NO:972.

39. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 150 contiguous nucleotides of the polynucleotide of claim 29.

45. (Amended) An isolated polynucleotide comprising at least [15] 35 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:973, a degenerate variant of SEQ ID NO:973, and a complement of SEQ ID NO:973.

47. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 35 contiguous nucleotides of the polynucleotide of claim 45.

53. (Amended) An isolated polynucleotide comprising at least [15] 100 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:1128, a degenerate variant of SEQ ID NO:1128, and a complement of SEQ ID NO:1128.

55. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 100 contiguous nucleotides of the polynucleotide of claim 53.

61. (Amended) An isolated polynucleotide comprising at least [15] 100 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:1192, a degenerate variant of SEQ ID NO:1192, and a complement of SEQ ID NO:1192.

63. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 100 contiguous nucleotides of the polynucleotide of claim 61.

69. (Amended) An isolated polynucleotide comprising at least [15] 150 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:1254, a degenerate variant of SEQ ID

NO:1254, and a complement of SEQ ID NO:1254.

71. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 150 contiguous nucleotides of the polynucleotide of claim 69.

77. (Amended) An isolated polynucleotide comprising at least [15] 35 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:1290, a degenerate variant of SEQ ID NO:1290, and a complement of SEQ ID NO:1290.

79. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 35 contiguous nucleotides of the polynucleotide of claim 77.

85. (Amended) An isolated polynucleotide comprising at least [15] 100 contiguous nucleotides of a nucleotide sequence [having at least 90% sequence identity to a sequence] selected from the group consisting of: SEQ ID NO:1492, a degenerate variant of SEQ ID NO:1492, and a complement of SEQ ID NO:1492.

87. (Amended) An isolated antisense nucleic acid molecule comprising at least [15] 100 contiguous nucleotides of the polynucleotide of claim 85.